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# Improvement of Right Ventricular Hemodynamics with Left Ventricular Endocardial Pacing during Cardiac Resynchronization Therapy

EOIN R. HYDE, Ph.D.,\*,† JONATHAN M. BEHAR, M.R.C.P.,\*,†,‡ ANDREW CROZIER, Ph.D.,\* SIMON CLARIDGE, M.R.C.P.,\*,† TOM JACKSON, M.R.C.P.,\*,† MANAV SOHAL, M.R.C.P.,\*,† JASWINDER S. GILL, M.D.,\*,† MARK D. O'NEILL, M.D.,\*,† REZA RAZAVI, M.D.,\* STEVEN A. NIEDERER, Ph.D.,\* and CHRISTOPHER A. RINALDI, M.D.,†

From the \*Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK; and †Department of Cardiology, Guy's and St. Thomas' NHS Foundation Trust, London, UK

**Background:** Cardiac resynchronization therapy (CRT) with biventricular epicardial (BV-CS) or endocardial left ventricular (LV) stimulation (BV-EN) improves LV hemodynamics. The effect of CRT on right ventricular function is less clear, particularly for BV-EN. Our objective was to compare the simultaneous acute hemodynamic response (AHR) of the right and left ventricles (RV and LV) with BV-CS and BV-EN in order to determine the optimal mode of CRT delivery.

**Methods:** Nine patients with previously implanted CRT devices successfully underwent a temporary pacing study. Pressure wires measured the simultaneous AHR in both ventricles during different pacing protocols. Conventional epicardial CRT was delivered in LV-only (LV-CS) and BV-CS configurations and compared with BV-EN pacing in multiple locations using a roving decapolar catheter.

**Results:** Best BV-EN (optimal AHR of all LV endocardial pacing sites) produced a significantly greater RV AHR compared with LV-CS and BV-CS pacing ( $P < 0.05$ ). RV AHR had a significantly increased standard deviation compared to LV AHR ( $P < 0.05$ ) with a weak correlation between RV and LV AHR (Spearman  $r_s = -0.06$ ). Compromised biventricular optimization, whereby RV AHR was increased at the expense of a smaller decrease in LV AHR, was achieved in 56% of cases, all with BV-EN pacing.

**Conclusions:** BV-EN pacing produces significant increases in both LV and RV AHR, above that achievable with conventional epicardial pacing. RV AHR cannot be used as a surrogate for optimizing LV AHR; however, compromised biventricular optimization is possible. The beneficial effect of endocardial LV pacing on RV function may have important clinical benefits beyond conventional CRT. (PACE 2016; 00:1–11)

**cardiac resynchronization therapy, ventricular contractility, endocardial pacing, biventricular acute hemodynamic response**

## Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for symptomatic heart failure (HF) patients with significantly impaired left ventricular (LV) function and prolonged QRS duration; however, 30–40% of patients fail to derive clinical benefit.<sup>1</sup> Attempts to improve CRT response have focused on improving both preprocedural<sup>2–5</sup> and intraprocedural<sup>6–8</sup> predictors of response, as well as alternate forms of CRT delivery.<sup>9–12</sup>

LV acute hemodynamic response (AHR) is a frequently used tool for CRT clinical research studies. Improvements in LV and/or right ventricular (RV) hemodynamics with CRT have been demonstrated<sup>13–16</sup>; however, the latter are often neglected with respect to CRT optimization.

\*These authors contributed equally to the production of this manuscript.

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Address for reprints: Steven A. Niederer, Ph.D., Division of Imaging Sciences and Biomedical Engineering, St. Thomas' Hospital, King's College London, SE1 7EH, UK. Fax: 0044-0-207-188-5442; e-mail: steven.niederer@kcl.ac.uk

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Furthermore, the RV AHR has been shown to positively correlate with cardiac index, which supports the hypothesis that improvement of this acute metric may have an important and positive contribution on cardiac output.<sup>14</sup> It is biologically plausible that biventricular (BV) optimization with simultaneous attention to the hemodynamic changes in both ventricles may be clinically beneficial. Biventricular endocardial pacing (BV-EN) has been shown to improve LV AHR compared to epicardial pacing<sup>11,12,17,18</sup>; however, the effect of BV-EN on RV AHR is less clear. A recent canine study demonstrated that the RV myocardium plays a key role in work redistribution and improved LV pump function with CRT but RV AHR was not significantly improved by LV-only or BV epicardial pacing,<sup>19</sup> despite simultaneous increases in LV AHR. However, the effect of BV-EN pacing on RV AHR was not addressed in that study.

The aim of the current study was to investigate the effect of epicardial and endocardial CRT on simultaneous RV and LV AHR. We hypothesized that: (1) BV-EN has a greater capacity to improve RV AHR more than conventional epicardial pacing; and (2) RV AHR could also be optimized concurrently to LV AHR, resulting in improved overall cardiac function. To test these hypotheses, and to investigate if RV AHR could be used as a surrogate for LV AHR, we performed a comparison of BV AHR to various pacing protocols including epicardial pacing via the coronary sinus in LV-only (LV-CS) and biventricular modes (BV-CS) as well as BV-EN.

### Methods

This study complies with the Declaration of Helsinki, the protocol was approved by the local ethics committee, and informed consent was obtained from each patient. Ten patients with conventional CRT criteria (New York Heart Association [NYHA] Class II–IV drug refractory HF, LV ejection fraction  $\leq 35\%$ , and QRS  $\geq 120$  ms) with previously implanted CRT systems, were recruited for an acute electrophysiology/pacing study. Patients were intentionally selected with a phenotype of suboptimal response to CRT as they have the most to gain by alternate strategies: Male patients with ischemic etiology and QRS duration 120–150 ms.<sup>20</sup> Patients with a mechanical aortic valve or significant peripheral vascular disease were excluded.

Baseline assessment prior to original implant included clinical assessment (NYHA functional class), 12-lead electrocardiogram, and 2D echocardiography (echo). Etiology of HF was confirmed on the basis of clinical history, coronary angiography, and cardiac magnetic resonance (CMR) imaging. An improvement of ventricular

AHR by  $>10\%$  defined an acute hemodynamic responder.<sup>6</sup>

### Invasive Hemodynamic Study

Patients underwent an invasive study at least 3 months following implantation of the CRT device. Light sedation was used and a steerable 6F Livewire decapolar catheter (St. Jude Medical St. Paul, MN, USA) was passed via the femoral artery retrogradely to perform endocardial pacing from multiple sites within the LV cavity. Intravenous heparin (70 U/kg) was administered to achieve systemic anticoagulation (target-activated clotting time 300–350 seconds). A 0.014-inch diameter high-fidelity Certus PressureWire (St. Jude Medical) was placed retrogradely into the LV cavity via the femoral or radial artery to assess real-time mean LV dPdtmax using the accompanying PhysioMon software (RADI Medical Systems, part of St. Jude Medical). An RV pressure wire was inserted via cannulation of the femoral vein and catheterization of the right heart to measure simultaneous RV dPdtmax. Atrial pacing (or RV pacing for atrial fibrillation) at 5–10 beats/min above the intrinsic rate was used as the baseline and was a constant for each patient throughout different pacing modes. At least 20 seconds was respected after any change in pacing protocol, in order to achieve hemodynamic stabilization prior to recording pressure measurements for 20 seconds. The mean dPdtmax for each pacing protocol was determined by averaging the dPdtmax over the recorded period following removal of beats affected by ventricular extra systoles (Fig. S1). The AHR was defined to be the percentage change in the maximal increase in the rate of change of pressure (denoted dPdtmax) with the intervention protocol as compared with its associated baseline protocol. To minimize the known effect of baseline drift in dPdtmax throughout the case, the baseline was reassessed prior to every change in pacing modality.

The sensed and paced atrioventricular (AV) and ventriculo-ventricular (VV) settings of the device were optimized using echocardiography, 6 weeks after the original implantation; the mean of these values is shown in Table I. For the acute pacing study, a set AV delay of 100 ms was used for all patients. No AV or VV optimization was performed during this study due to the added time these require, and our intention to focus on endocardial pacing from multiple locations (VV pacing was simultaneous in all patients). Mean and standard deviation (SD) pressure metrics were also recorded for each heartbeat including the averaged peak systolic pressure (maximum pressure per beat), start diastolic pressure (minimum pressure per beat), and end diastolic

**Table I.**

Baseline Demographics, Device Settings, and CRT Response

**Demographics****Pre-CRT implantation**

Mean age (years)	70 ± 7
Male	9 (100%)
Sinus rhythm	6 (67%)
Ischemic heart disease	7 (78%)
QRS duration (ms)	152 ± 37
LBBB morphology	9 (100%)
NYHA class III	7 (78%)
LV systolic function, EF by echo (%)	30 ± 8
RV systolic function: TAPSE (mm)	13 ± 4
RV basal diameter, diastole (mm)	41 ± 8
RV systolic function, EF by MRI (%)	43 ± 10

**CRT settings**

Sensed AV delay (ms)	120 ± 22
Paced AV delay (ms)	135 ± 15
VV timing: LV ahead (ms)	17 ± 13

**CRT response assessment at 6 months**

LV systolic function, EF by echo (%)	32 ± 11
RV systolic function: TAPSE (mm)	14 ± 2
RV basal diameter, diastole (mm)	39 ± 10
Echo responder	3 (33%)
Clinical responder	5 (56%)

Averaged data are mean ± SD.

AV = atrio-ventricular; CRT = cardiac resynchronization therapy; ECHO = echocardiography; EF = ejection fraction; LBBB = left bundle branch block; LV = left ventricular; MRI = magnetic resonance imaging; NYHA = New York Heart Association; RV = right ventricular; TAPSE = Tricuspid Annular Plane Systolic Excursion; VV = ventricular-ventricular.

pressure, which was defined to occur when the rate of increase of pressure traversed 100 mm Hg/s.

**Pacing Protocols**

Baseline dPdtmax was compared with paced dPdtmax for the following pacing protocols:

1. LV-only epicardial CRT using the implanted LV lead (LV-CS);
2. BV epicardial CRT using the RV lead and the implanted LV lead (BV-CS);
3. BV endocardial pacing using the RV lead and the roving LV decapolar catheter (BV-EN) in multiple positions at random.

**BV AHR Optimization**

BV AHR optimization involved a review of paired LV and RV AHR data in order to

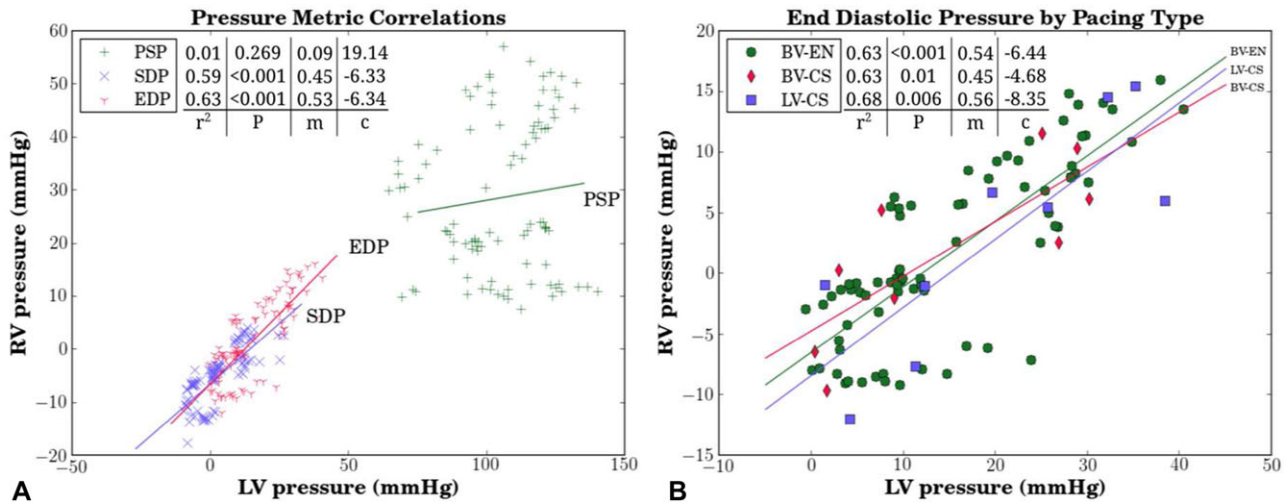
delineate the optimal protocols for both ventricles simultaneously. As conventional CRT optimization by AHR maximizes LV AHR only, BV AHR optimization (incorporating both LV and RV AHR metrics) will almost certainly involve some decrease in LV AHR. We therefore adhered to the following principle when selecting BV AHR optimization: the increase in RV AHR must be greater than the decrease in LV AHR, compared with the maximal LV AHR protocol (Fig. S2), as the effect of RV dPdtmax on RV function and subsequent clinical outcome is less clear than that of the LV.

To construct a BV optimization metric, which must be relative to the response achieved by the maximal LV AHR protocol, we denote the response achieved by conventional AHR and BV AHR optimization with subscripts LV and BV, respectively, and the comparative change in ventricular AHR from that of the maximal LV AHR protocol by  $\Delta LV = (LV\ AHR)_{BV} - (LV\ AHR)_{LV}$  and  $\Delta RV = (RV\ AHR)_{BV} - (RV\ AHR)_{LV}$ . Then it is proposed to use the ratio of the change in RV AHR ( $\Delta RV$ ) to the absolute change in LV AHR ( $|\Delta LV|$ ), giving the ratio  $\Delta RV/|\Delta LV|$ , as a quantitative measure of BV AHR performance relative to the conventional optimization method. This metric is applied to all protocols that did not maximize LV AHR and a protocol is deemed to be a viable alternative to the conventionally chosen protocol when the metric value is  $>1$ . The viable protocol that maximizes this BV AHR optimization metric is the chosen alternative BV optimization protocol. Conceptually, if one considers the set of points given by the relative response of a protocol compared to the maximal LV AHR protocol in the *LV AHR*, *RV AHR* Cartesian plane, then this process selects the protocol with the largest negative slope of the line joining the compromise protocol datum to the origin (Fig. S2).

**Statistical Methods**

Statistical quantities were computed using MATLAB (R2013b, The MathWorks, Cambridge, MA, USA). Values were presented as numbers and percentages for discrete variables and as mean ± SD for continuous variables. Bivariate correlations were quantified using both Pearson's parametric correlation coefficient ( $r_p$ ) and Spearman's nonparametric rank-order correlation coefficient ( $r_s$ ). One-way balanced repeated measures analysis of variance (ANOVA) was used to test for significant effects of the three pacing methods (LV-CS/BV-CS/best BV-EN) on baseline hemodynamics, where "best BV-EN" denotes maximal endocardially paced AHR for each patient averaged over all patients, as opposed





**Figure 1.** Scatterplot of paced LV and RV pressure data acquired from nine patients undergoing various pacing protocols (LV only-coronary sinus = LV-CS; biventricular-coronary sinus = BV-CS; biventricular endocardial pacing = BV-EN). (A) Peak systolic (PSP), start diastolic (SDP), and end diastolic (EDP) pressures. Simple linear regression was applied to each pressure metric (m-slope; c-intercept). (B) Detailed analysis of EDP by pacing type. LV = left ventricular; RV = right ventricular.

to “average BV-EN,” which denotes the mean endocardially paced AHR-AHR for each patient averaged over all patients. Pairwise analysis for differences between epicardial pacing strategies (LV-CS/BV-CS) and endocardial pacing (best BV-EN/average BV-EN) was performed using a two-tailed Student’s *t*-test. A P-value <0.05 was considered statistically significant for all analyses.

## Results

### Patient Demographics (Table I)

Nine datasets were included in the analysis due to the recurrent dislodgement of the RV pressure wire during one procedure. The distribution of CRT devices was as follows: St. Jude Medical Quadra Assura (n = 3); Promote Quadra (n = 5); and Medtronic Consulta (n = 1). The mean age was  $70 \pm 7$  years, mean QRS duration was  $152 \pm 37$  ms, and all patients had left bundle branch block (LBBB). The majority of participants had cardiomyopathy secondary to ischemic heart disease (78%) and were in sinus rhythm (67%). Patients had impairment of both LV and RV systolic function prior to device implantation. Mean LV ejection fraction was  $30 \pm 8\%$ , mean Tricuspid Annular Plane Systolic Excursion (TAPSE) was  $13 \pm 4$  mm (normal > 16 mm<sup>21</sup>), mean RV basal diameter was  $41 \pm 8$  (normal < 42 mm<sup>21</sup>), and mean RV systolic function measured with CMR was  $43 \pm 10\%$  (normal range 40–68%). The mean time from CRT implantation to

study participation was  $15 \pm 15$  months. Patients were assessed for CRT response at 6 months following implantation. Response was determined using the Packer clinical composite score<sup>22</sup> and with 2D echo, whereby an echo responder was defined as a patient with  $\geq 15\%$  reduction in end systolic volume. This cohort of patients had a high proportion of CRT nonresponse, six of nine (67%) as measured by echo and four (45%) as measured by clinical composite score. Endocardial pacing was performed in several positions from base to apex in each patient in a random fashion. The mean number of endocardially paced positions per patient was  $8.4 \pm 3.7$  (Table S1).

### Correlation of Interventricular Pressure and AHR Metrics

Biventricular and patient-specific measurements of peak systolic pressure, start diastolic pressure, and end diastolic pressure are presented in Table S2 in the Supporting Information. RV and LV start and end diastolic pressure measurements displayed a positive correlation (start:  $r_p = 0.77$ ,  $r_s = 0.84$ ; end:  $r_p = 0.79$ ,  $r_s = 0.82$ ). Simple linear regression analysis of the start and end diastolic pressure relationships yielded coefficients of determination of  $r^2 = 0.59$  and  $r^2 = 0.63$ , respectively (Fig. 1). Compared to the diastolic pressure measurements, peak systolic pressures had a reduced positive correlation ( $r_p = 0.11$ ,  $r_s = 0.12$  [Table S2]) and a reduced linear model coefficient of determination of  $r^2 =$

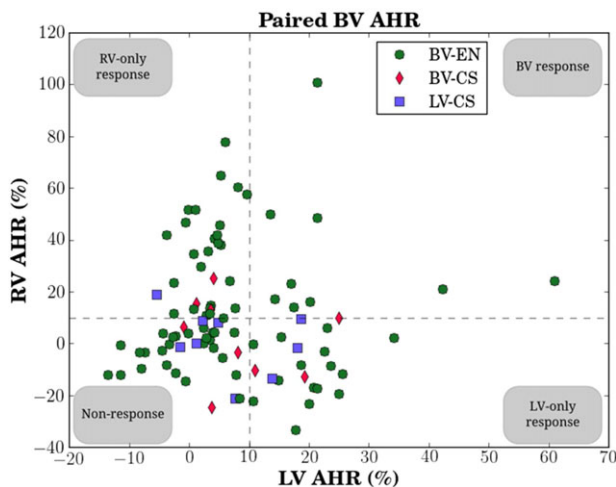
**Table II.**

Correlation between RV and LV AHR

ID	LV AHR(%)		RV AHR(%)		Correlations	
	Maximum	Average	Maximum	Average	$r_p$	$r_s$
1	3.9	$-1.0 \pm 3.7$	15.3	$4.2 \pm 7.2$	0.56	0.54
2	61	$19.5 \pm 18.9$	24.1	$1.3 \pm 14.4$	0.79	0.72
3	34.2	$10.3 \pm 9.6$	51.7	$9.7 \pm 23.6$	-0.04	-0.14
4	14.3	$5.1 \pm 4.3$	57.5	$24.3 \pm 24.9$	0.08	0.05
5	13.8	$6.2 \pm 3.9$	65.1	$32.8 \pm 24.0$	-0.19	0.19
6	25.6	$17.6 \pm 7.5$	6	$-10.9 \pm 10.9$	-0.41	-0.25
7	7.6	$0.3 \pm 5.7$	18.9	$6.8 \pm 9.1$	0.40	0.37
8	21.4	$0.2 \pm 8.9$	101	$25.0 \pm 35.5$	0.77	0.76
9	25	$12.4 \pm 11.1$	9.9	$4.1 \pm 5.7$	0.91	1.00
All	61	$7.6 \pm 11.7$	101	$10.6 \pm 24.4$	0.00	-0.06

Comparison of interventricular sensitivity of AHR across all pacing protocols (BV-CS, LV-CS, and BV-EN). Individual and whole-cohort maximum and averaged AHR (mean  $\pm$  SD) were calculated for both ventricles.

AHR = acute hemodynamic response; ID = anonymized patient number;  $r_p$  = Pearson's correlation coefficient;  $r_s$  = Spearman's rank correlation coefficient. SD = standard deviation. Other abbreviations as in previous tables.



**Figure 2.** Scatterplot of all paired LV-RV AHR data for nine patients, split by conventional coronary sinus pacing (a single protocol of LV-CS/BV-CS for each patient) and BV endocardial pacing (BV-EN) protocols at multiple locations per patient. An AHR value  $>10\%$  above baseline was used as the benchmark for a positive AHR, as indicated by the dashed lines.<sup>6</sup> Using this cutoff, data points are thus divided into LV-only response, RV-only response, BV response, and nonresponse. AHR = acute hemodynamic response. Other abbreviations as in Figure 1.

0.013 (Fig. 1A). Overall, LV and RV AHR were poorly correlated as can be qualitatively seen by the nonlinear distribution of data in Figure 2, and is quantitatively demonstrated by the correlation

coefficient cohort averages of  $r_p = 0.005$  and  $r_s = -0.055$  (Table II). The lack of a linear relationship between LV and RV AHR was also displayed on an individual basis (Fig. S3) as demonstrated by the wide range of patient-specific correlation values of Table II.

#### Comparison of Epicardial versus Endocardial CRT on BV AHR (Table III and Figs. 3 and 4)

LV AHR was improved by  $8.4 \pm 8.7\%$  from baseline by BV-CS ( $P = 0.02$ ) and  $6.6 \pm 8.6\%$  by LV-CS ( $P = 0.051$ ) (Table III). Notably, RV AHR was not improved by either BV-CS ( $2 \pm 15.9\%$ ,  $P = 0.712$ ) or LV-CS ( $0.9 \pm 12.3\%$ ,  $P = 0.832$ ). The best BV-EN, however, produced significantly improved AHR for both ventricles compared with conventional epicardial pacing (Fig. 3). The average LV and RV increase in AHR with BV-EN was  $21.4 \pm 16.6\%$  and  $37.1 \pm 31.8\%$ , respectively (Fig. 3). In a pairwise comparison of pacing methods, best BV-EN was a significant improvement in terms of RV AHR over BV-CS ( $P = 0.021$ ) and LV-CS ( $P = 0.02$ ). Best BV-EN was also a significant improvement in terms of LV AHR over LV-CS ( $P = 0.04$ ) but not BV-CS ( $P = 0.065$ ).

The average SD of RV AHR across all patients was greater than that of the LV ( $\pm 18\%$  vs  $\pm 8\%$ ). The SD for the RV AHR under all three pacing methods was larger than the SD of the equivalent LV AHR (Fig. 3).

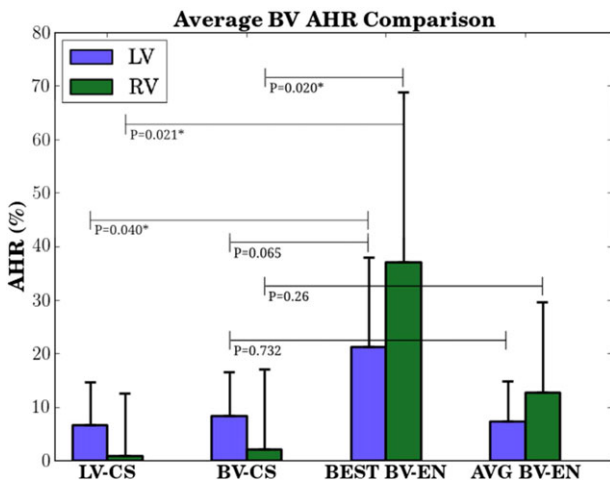
A patient-specific comparison of the BV AHR performance of best epicardial and best endocardial pacing under conventional LV AHR

**Table III.**

Hemodynamic Data from HF and LBBB Patients (n = 9) during Baseline and CRT Pacing

Variable	Baseline	LV-CS	BV-CS	BV-EN	ANOVA (P-Value)
LV start diastolic pressure (mm Hg)	5.2 ± 11.9	5.5 ± 11.9	4.0 ± 10.4	5.3 ± 11.0	0.992
LV end diastolic pressure (mm Hg)	19.0 ± 15.4	20.1 ± 13.6	14.8 ± 12.7	19.8 ± 11.8	0.822
LV peak systolic pressure (mm Hg)	103.2 ± 19.8	103.6 ± 19.7	102.2 ± 18.5	107.3 ± 18.2	0.948
LV dPdtmax (mm Hg/s)	808.1 ± 247.2	856.2 ± 252.9	863.1 ± 243.4	989.5 ± 290.4	0.501
LV AHR (%)	0.0 ± 0.0	6.6 ± 8.6	8.4 ± 8.7	21.3 ± 17.6	0.036
RV start diastolic pressure (mm Hg)	-5.1 ± 6.2	-5.2 ± 6.8	-4.4 ± 5.2	-3.6 ± 5.5	0.933
RV end diastolic pressure (mm Hg)	1.7 ± 8.4	2.9 ± 9.3	2.0 ± 7.2	3.8 ± 7.9	0.946
RV peak systolic pressure (mm Hg)	29.4 ± 16.4	28.6 ± 15.5	30.1 ± 15.9	32.4 ± 15.6	0.961
RV dPdtmax (mm Hg/s)	341.4 ± 91.3	348.1 ± 107.5	348.2 ± 96.2	453.1 ± 173.3	0.176
RV AHR (%)	0.0 ± 0.0	0.9 ± 12.3	2.0 ± 15.9	35.0 ± 32.3	0.004

AHR = acute hemodynamic response; ANOVA = analysis of variance; BV-CS = biventricular coronary sinus pacing; BV-EN = biventricular endocardial pacing; HF = heart failure; LV-CS = left ventricular coronary sinus pacing. Other abbreviations as in previous tables.

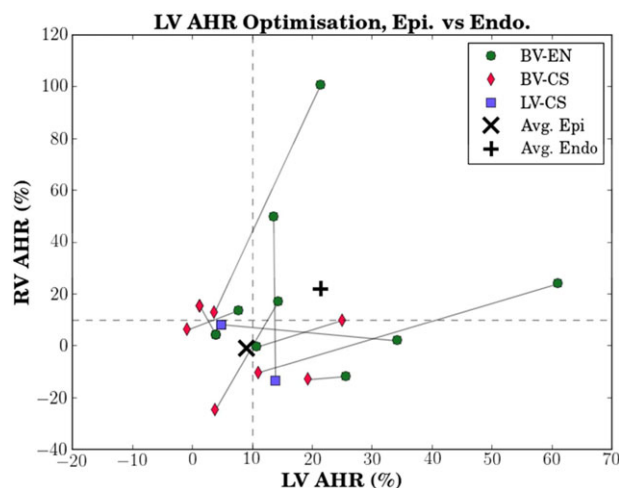


**Figure 3.** Bar chart (mean ± SD) comparing mean BV AHR resulting from LV coronary sinus (LV-CS, n = 9), BV coronary sinus (LV-CS, n = 9), and BV endocardial (BV-EN, n = 76) pacing. Best BV-EN significantly improved ventricular AHR over LV-CS for both ventricles and over BV-CS for the right ventricle. There was no statistical difference between LV-CS and BV-CS for either ventricle, nor was there a statistical difference between CS pacing and the average BV-EN AHR for either ventricle. \* denotes statistically significant. SD = standard deviation. Other abbreviations as in previous figures.

optimization is presented in Figure 4. For epicardial pacing (LV-CS/BV-CS) and with respect to AHR (10% cutoff), there were three nonresponders, two RV-only responders, four LV-only responders, and zero BV responders. The average AHR for epicardial pacing was 9.1% and -1% for the LV and RV, respectively. For endocardial pacing (BV-EN) and with respect to AHR, there was one nonresponder, one RV-only responder, three LV-only responders, and four BV responders. The average AHR for best BV-EN pacing increased relative to epicardial pacing to 21.3% and 22.2% for the LV and RV, respectively. Overall, best BV-EN as opposed to epicardial pacing increased the number of LV responders by 22% and the number of RV responders by 33%.

### Biventricular Hemodynamic Optimization (Fig. 5)

BV-EN produced 77% of the patient-specific best LV AHR pacing protocols. Using the aforementioned BV AHR optimization metric, 56% patients had an alternative viable protocol (Table S3). Conventional LV AHR optimization resulted in one nonresponder, one RV-only responder, four LV-only responders, and three BV responders. In contrast, our alternative BV AHR optimization method resulted in zero nonresponders, three RV-only responders, two LV-only responders, and four BV responders. The

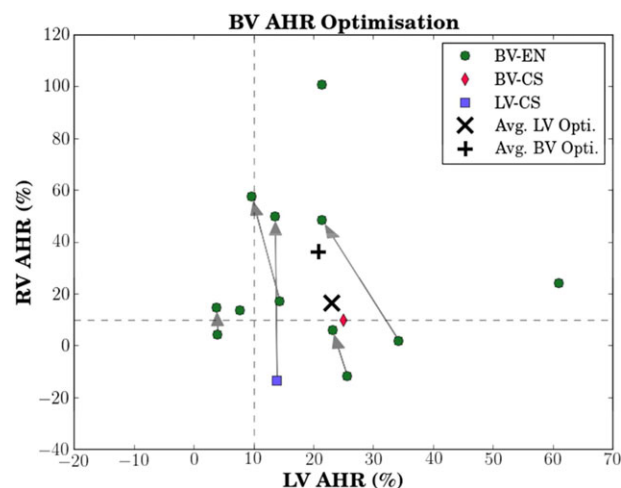


**Figure 4.** Patient-specific paired biventricular AHR data using LV AHR data alone to find the best epicardial (LV-CS or BV-CS) pacing protocol and the best endocardial (BV-EN) protocol per patient (plotted with its associated RV AHR). The resulting endocardial-epicardial BV AHR pair for each patient is connected by the gray solid line. An AHR value  $>10\%$  above baseline was used as the benchmark for a positive AHR, as indicated by the dashed lines.<sup>6</sup> Mean of the best epicardial protocols (by LV AHR alone) show minimal/no change in RV-AHR ( $\sim 0\%$ ) with approximately 10% improvement in LV AHR (X). This compared with a  $+21\%$  improvement in LV AHR and similar improvement in the paired RV AHR with the mean of best endocardial protocols (+). Seven of nine patients improved LV AHR with BV-EN compared to CS pacing. The axes are scaled differently. Abbreviations as in previous figures.

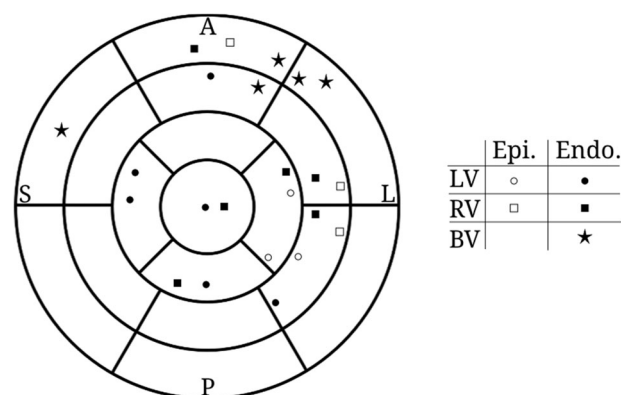
averaged LV-optimized AHR was 23% and 16% for the LV and RV, respectively, which can be compared with the averaged BV-optimized AHR of 21% and 36% for the LV and RV, respectively. Thus, BV AHR optimization resulted in a greater than twofold increase in mean RV AHR at the relatively minor expense of an approximately 2% decrease in mean LV AHR compared to LV-only AHR optimization.

#### Optimal LV Pacing Site Location (Fig. 6)

The optimal site for the LV lead whilst delivering BV pacing was highly patient-specific, scattered across most regions of the myocardium whether the optimal LV AHR alone or RV AHR alone was used. Where viable alternative BV optimization protocols existed, four of five (80%) had the LV lead position clustered in the basal-mid- anterolateral position. LV lead positions were endocardial in 12 of 18 cases when looking at the



**Figure 5.** Alternative, patient-specific biventricular AHR optimization. Here, the best patient protocol selected using LV AHR are compared to an alternative, BV AVR optimization protocol and connected by arrows where a viable alternative exists (five out of nine; Table A3). BV endocardial protocols were optimal in seven of nine (eight out of nine) cases under conventional (BV) optimization. The axes are scaled differently. Abbreviations as in previous figures.



**Figure 6.** 17-Segment American Heart Association plot displaying the approximate location and pacing type (epicardial or endocardial) of the maximal achieved AHR for the LV (circle), RV (square), and BV (star; see Fig. 5). Note that four of nine patients did not have a viable compromise protocol for BV AHR optimization. Abbreviations as in previous figures.

optimal AHR (LV AHR alone,  $n = 9$  and RV AHR alone,  $n = 9$ ); the remaining six of 18 cases were in an epicardial position.

#### Discussion

To our knowledge, this study is the first to simultaneously analyze the effect of epicardial and



endocardial pacing on LV and RV AHR in humans. The principal findings were:

1. Best BV-EN produced a significant improvement in the AHR of both ventricles compared with conventional epicardial pacing;
2. Compromise optimization is possible and may be helpful in the improvement of overall biventricular function, i.e., by accepting a small reduction in LV AHR, a relatively greater improvement in RV AHR can often be achieved;
3. The measurement of RV AHR is more sensitive to pacing perturbations than LV AHR;
4. A weak correlation exists between the RV and LV AHR, thus the former cannot be used as a surrogate for the latter.

CRT is an efficacious therapy for selective patients with HF, yet this treatment is associated with a significant nonresponse rate. Reasons for poor response to CRT are well documented,<sup>23</sup> including incomplete resynchronization leading to persistent dyssynchrony and suboptimal lead placement. While alternative epicardial pacing strategies are being considered,<sup>24</sup> LV endocardial stimulation is increasingly being investigated as it has several advantages over conventional epicardial pacing: (1) there is no access constraint to myocardial sites subtended by the CS, which is important given the significant individual variation with regard to the optimal LV pacing site<sup>10,18</sup>; (2) endocardial pacing produces more physiological activation of the LV and more favorable tissue repolarization.<sup>25,26</sup> Our findings are in keeping with previous clinical studies, which suggest that endocardial pacing produces a superior LV AHR compared with epicardial pacing, and that LV AHR is highly site-specific.<sup>3,18,27</sup> Indeed, patients with a suboptimal response to conventional CRT have been demonstrated to show both clinical and echocardiographic improvement from endocardially delivered LV stimulation for BV pacing.<sup>28</sup>

Importantly, our results suggest that the superior acute hemodynamic effects of endocardial pacing over conventional epicardial CRT may be extended to the RV as well (Fig. 2). As expected, the mean of the best achievable LV AHR increased from conventional epicardial BV pacing to endocardial BV pacing (Fig. 4). In addition, this increase was accompanied with a rise in the corresponding RV AHR inferring that some of the beneficial effects of biventricular pacing could be mediated through improvement in RV function.

### Comparison with Previous Studies

The similar improvement in LV AHR with LV-CS or BV-CS configurations (Fig. 3) is in

keeping with the findings of Lumens et al.<sup>19</sup> Using computational modeling and experimental hemodynamic measurements in canines, they showed a nonsignificant difference in LV AHR improvement between LV-CS and BV-CS pacing, and a nonsignificant improvement in RV AHR from either epicardial pacing mode.<sup>19</sup> The additional application of BV-EN pacing in this study produced a substantial increase in maximal RV AHR, which may be linked to an enhanced ability to redistribute myocardial fiber work by altering the endocardial pacing location.<sup>19</sup>

The greater increase in RV AHR from BV-EN as opposed to epicardial pacing is contrary to the findings of the acute LBBB canine model study of van Deursen et al.<sup>25</sup> where only BV epicardial pacing led to a statistically significant increase in RV AHR. Several key factors may explain these seemingly opposing findings: (1) interspecies differences (canine vs human); (2) pericardial pressure differences—the canine experiment was performed in open-chest dogs with the pericardium removed, whereas this study was conducted *in vivo* via cardiac catheterization; and (3) disease state—the canines were acute radiofrequency-ablated LBBB models, whereas the study participants were chronic HF patients with long-term implanted CRT devices (Table I).

We have shown for the first time that compromise BV optimization can be performed and may be useful in selected patients. Out of nine patients, five were found to have a viable BV-optimized pacing response. While 77% (seven out of nine) of patients achieved maximal LV AHR from BV-EN, this proportion increased to 88% (eight out of nine) when the alternative BV hemodynamics optimization was retrospectively applied (Fig. 5); thus, the ability to increase BV hemodynamic function appears to be feasible with endocardial pacing. BV optimization resulted in an average increase of RV AHR by 20% at the expense of only a 2% decrease in LV AHR, compared to conventionally optimized AHRs.

### Clinical Relevance

AHR is an accurate reflection of acute pump function but whether changes in maximum dP/dt translate into better clinical outcomes is yet to be proven in a large-scale study. Our group is currently conducting a multicenter, international, randomized study (RADI CRT – NCT 01464502) to formally assess this. Whatever the outcome, an intra-arterial measurement as a predictive tool nonetheless carries a risk of thromboembolic stroke. Thus it would be clinically advantageous to circumvent this risk by using a surrogate, such as the RV AHR. Our data, however, suggest that a

weak correlation exists between LV AHR and RV AHR and does not support the use of RV AHR as a surrogate for LV function. This weak correlation may be due to an increased sensitivity of the RV AHR to pacing perturbations compared to the LV AHR (Fig. 3).

Endocardial pacing can increase not only the average LV AHR but also the corresponding RV AHR over epicardial pacing, and therefore incorporation of BV optimization to identify the optimal position for the LV lead may translate into improved long-term clinical outcomes. However, if adopting a BV AHR approach, it is unknown what reduction in LV AHR, if any, is acceptable in order to improve RV AHR and maintain a positive clinical outcome. For example, ambiguity exists with patient no. 3 (Table S3 and Fig. 5) where an alternative viable protocol results in a reduction of LV-AHR from 34% to 21% while increasing RV AHR from 2% to 49%. A larger clinical study to examine the long-term clinical outcomes of BV optimization and the relationship between LV and RV AHR would be needed, and should include a thorough investigation of the clinical relevance of more complex BV optimization metrics than the simple metric adopted in this study.

### Study Limitations

We intentionally selected ischemic patients for whom response to CRT was suboptimal; this clearly leads to selection bias, however, this patient group has the most to gain from alternate pacing strategies and incorporation of different AHR protocols (such as using the RV AHR in combination with the LV AHR rather than the latter alone).

Although we have studied a small number of patients, we have a large number of data points within this group, which we believe provides sufficient information for analysis and has resulted in statistically significant findings. Only limited substrate data were available and therefore we did not investigate the relationship between acute response and myocardial fibrosis, which is known to affect clinical outcomes from CRT.<sup>29</sup> The AHRs reported in these patients are on average 15 months after CRT implantation. It is known that LV remodeling (whether positive or negative)

often occurs between 3–6 months<sup>6</sup>; thus, AHR values at 15 months are unlikely to be the same as those at implantation and caution needs to be applied in the extrapolation of these findings to patient AHR at the time of implant. We also acknowledge that as a result of the anatomical restrictions of the coronary veins, we have more data points with endocardial pacing and therefore had a greater opportunity to achieve a better AHR with endocardial pacing.<sup>30</sup> However, our results are similar to published data suggesting that endocardial pacing involves access to the fast-conducting His-Purkinje tissue and may be a preferential location for LV stimulation in delivering CRT.<sup>25,26,31</sup>

An important assumption of the current manuscript is that a higher RV dPdtmax equates with an improvement in RV function. In support of this there are published data that the RV AHR positively correlates with the cardiac index supporting the hypothesis that improvement in this acute metric may have a positive and important contribution on cardiac output.<sup>14</sup> It should be acknowledged, however, that this may not necessarily be the case in all HF patients where a decrease in LV function may lead to an increase in RV afterload and so higher RV pressure may not necessarily be a positive sign. Similarly the right side of the heart acts more as a volume and capacitance conduit than a high-pressure pump, which exists on the left side, and therefore, the interpretation of the concept of RV or BV optimization may not be straightforward. Our findings of a change in the relation between RV and LV dPdtmax do, however, highlight the fact that changes in LV function are linked to RV function and *vice versa*.

### Conclusions

BV-EN pacing has greater capacity to improve RV as well as LV AHR compared with conventional epicardial pacing. A new metric of compromised biventricular optimization, where RV AHR is increased for a relatively smaller decrease in LV AHR, is feasible with BV-EN pacing and may be of clinical benefit in patients with a poor CRT response to epicardial pacing. The weak correlation between LV and RV AHR across all tested pacing modes does not support the use of RV AHR as a surrogate measure of LV AHR.

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### Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1:** Patient-Specific Pacing Group Breakdown of the Total Dataset.

**Table S2:** Individualized Interventricular Pressure Metrics Correlations.

**Table S3:** Conventional and Alternative CRT Optimizations of Biventricular Function.

**Figure S1:** Example processing of an individual pacing protocol using our bespoke software “pTool.” This software allows for the rapid removal of ectopic beat effects from the analyzed dataset. Ectopic beats were observed to have an influence on one beat prior- and up to two beats postectopic; thus, data from these beats were selected for removal from data analysis (shaded beat windows). Quantities of interest in the remaining beat windows were then analyzed to produce protocol-averaged metrics (mean  $\pm$  standard deviation), e.g., peak systolic pressure, start diastolic pressure, end diastolic pressure, and dPdtmax.

**Figure S2:** The datum corresponding to the maximal LV AHR protocol is located at the bottom right hand corner of each panel (i.e., (0,0)); the BV AHR of all other protocols are located relative to this data point. Viable compromise protocols are those that lie in the white triangular region, i.e.,  $\Delta RV - \Delta LV$ , meaning that the enhanced RV response is greater than the diminished LV response. The vertical blue line indicates the 80% potential cutoff line as one possible strategy for selecting alternative protocols. Based on this BV optimized approach, three patients would have viable alternative protocols (patients 1, 5, and 6). AHR = acute hemodynamic response; BV = biventricular; LV = left ventricular; RV = right ventricular.

**Figure S3:** Scatterplot of all paired LV-RV AHR data. The number is anonymized patient identification, and the green, red, and lilac colors correspond to BV-EN, BV-CS, and LV-CS pacing, respectively. Acute ventricular response occurs for an AHR value  $>10\%$  (indicated by the dashed lines).<sup>6</sup> Note that patient 9 is the only patient not to improve via endocardial pacing as opposed to via the coronary sinus. This patient had the least number of endocardial protocols tested ( $n = 2$ ) compared to all other patients (Table S1). AHR = acute hemodynamic response; BV = biventricular; CS = coronary sinus; EN = endocardial; LV = left ventricular; RV = right ventricular.